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Effect of Steroid and High-Dose Immunoglobulin Therapy on Opsoclonus-Myoclonus Syndrome Occurring in Neuroblastoma

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The authors describe a case of an 8-month-old boy with opsoclonus-myoclonus syndrome (OMS) and coincident unresectable neuroblastoma (NB). He achieved a complete remission for NB after 6 courses of standard-dose chemotherapy without significant neurological improvement despite the use of steroids and high-dose immunoglobulin (HIG), administered separately. Only the combined treatment with these two drugs induced a complete disappearance of neurological symptoms. On the basis of this experience, the authors suggest the association of steroids plus HIG for the treatment of OMS in patients not responsive to conventional first line therapy with steroids. Med. Pediatr. Oncol. 30:15–17, 1998. © 1998 Wiley-Liss, Inc.

Key words: opsomyoclonus syndrome; neuroblastoma; treatment

INTRODUCTION

Opsoclonus-myoclonus syndrome (OMS) is a clinical entity characterized by opsoclonus, polymyoclonia, and ataxia, with acute or subacute onset, which occurs mostly in children under 3 years of age. It can be associated with either neuroblastoma (NB) or follow viral infections, or have no recognizable etiology [1–3].

The treatment of OMS is usually based on ACTH or steroids [1,3,4]. Recently, high-dose immunoglobulin (HIG) has been administered to some patients on the basis of an immunological etiology hypothesized for this syndrome, but results are controversial [5–8].

We report herein a case of a child with unresectable NB and OMS whose neurological symptoms responded very well to a combined treatment with steroids plus HIG.

CASE REPORT

An 8-month-old boy was referred to our institution 1 week after the acute onset of ataxia, opsoclonus, polymyoclonia, and irritability. Previous evaluation included a lumbar puncture and brain magnetic resonance imaging (MRI), both of which failed to show an abnormality. To search an occult NB, a total body computed tomographic (CT) scan was performed; it confirmed the presence of a calcified retroperitoneal mass in the lumbo-aortic region with extension to the intervertebral foramina without spinal cord compression; the aorta and inferior vena cava were encased by the tumor. Catecholamine urinary excretion was abnormally high for age (VMA 14.2 mg/day, $\geq$2.5 SD). A meta-iodobenzylguanidine (MIBG) [9] scintigraphy was positive only on the retroperitoneal region and no osseous metastases were detected. Surgical biopsy of the tumor revealed an unfavorable NB according to Shimada et al. [10], and four bone marrow aspirates performed at surgery were normal. The tumor was studied for MYCN amplification, DNA content, and loss of heterozygosity for the short arm of chromosome 1 without evidence of biomolecular or genetic abnormalities.

According to the International Neuroblastoma Staging System (INSS) [11], the patient was classified as stage 3 and treated, in consideration of age less than 1 year, with 6 courses of standard-dose chemotherapy consisting of vincristine, doxorubicin, and cyclophosphamide, as previewed by the Italian Neuroblastoma Protocol (NB 92). The child achieved a complete remission 6 months post-diagnosis; on the contrary, neurological symptoms did not disappear and required different therapeutic attempts to obtain a significant remission.

TREATMENT FOR OMS

At the onset of OMS, oral therapy with dexamethasone (0.9 mg/kg/day) was started in order to reduce neu-

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rological disabilities and to prevent possible sequelae, but after 3 months of treatment a full remission was not obtained and the child still presented with polymyoclonia and opsoconus. To avoid the side effects of a prolonged treatment with steroids, we decided to stop it and to administer HIG (400 mg/kg/day on 4 consecutive days), but there was no neurological improvement observed in the following days.

Because of the failure of steroids and HIG given as a single agent, we started a combined treatment with dexamethasone (0.1 mg/kg/day on alternate days) plus HIG 300 mg/kg/week for 1 month and then 300 mg/kg once a month. After 1 month the neurological recovery was quite complete, but different subsequent attempts to reduce the dosage of steroids or HIG always caused a worsening of neurological status, so at 20 months postdiagnosis the child is still in treatment. The present neurological status shows only increased tendon reflexes at the limbs without clear signs of OMS. Psychomotor development is normal for age (psychomotor quotient is 93 according to Brunet-Lézine scale). Presently no immunological dysfunction or other side effects correlated with the prolonged treatment were registered in our patient.

DISCUSSION

The current treatment of OMS is based on ACTH or steroids [1,3,4]; the majority of patients rapidly improved, but a complete and persistent remission is observed only in a small percentage [1,4]. Furthermore, the necessity of prolonged treatment with possible side effects is reported in the literature, as well as recurrence of OMS during steroid tapering or withdrawal. The pathophysiological basis of OMS in NB patients is still unclear; the hypothesis of an autoimmune mechanism seems to be attractive but is by no means established. The production of antibodies directly causing neurological dysfunction is a theory recently supported by Fisher et al. [5], who have isolated in the cerebral spinal fluid of one patient with OMS and NB an antibody called ''anti-Hu antineural,'' which has the capacity to cross-react with neuroblastic cells. On this basis, HIG administration has been adopted as in other immunomediated neurological diseases (myasthenia, inflammatory demyelinating polyneuropathy), but results are controversial [5–8]. In two patients reported by Sugie et al. [8] and Fisher et al. [5], a rapid improvement in OMS was obtained with HIG at doses ranging from 150 to 400 mg/kg/day for 3 or 4 consecutive days; in another case by Sheth et al. [7], a complete resolution of OMS was registered with a single course of HIG (500 mg/kg/day for 5 consecutive days). On the other hand, Penzien et al. [6] reported a complete failure of HIG in a patient treated with 200 mg/kg 3 times on alternate days.

However, all of these authors recommend this therapeutic attempt in cases of steroid failure given as first line therapy. In our case, neither steroids nor HIG administered as a single agent induced a complete disappearance of neurological symptoms that responded completely with their combined use; the synergistic effect of steroids and HIG is well known in the treatment of acute and chronic immune thrombocytopenic purpura [12], but to our knowledge this type of therapy has not yet been reported in OMS.

On the basis of our experience, we think that the association of the two drugs could represent a chance for treatment of OMS in those patients who do not achieve a complete and persistent neurological remission with conventional steroid therapy. Late effects of such a long-term treatment with steroids plus HIG are unknown; therefore, a careful clinical observation is required to prevent and minimize possible sequelae.

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